965-47 Comparison of Regional Myocardial Blood Flow and Metabolism in Patients with Ischemic and Non-ischemic Cardiomyopathy

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Myocardial viability and recovery of left ventricular (LV) function after revascularization is predicted by the presence of positron emission tomography (PET) defined F-18 deoxyglucose (FDG):blood flow mismatch pattern in patients with ischemic cardiomyopathy (ICM). However, little is known about regional blood flow and metabolism patterns in patients with non-ischemic cardiomyopathy (NICM). Therefore, we studied 10 symptomatic patients (NYHA class II and III) with left ventricular dysfunction; 5 had ICM and 5 NICM. All patients underwent radionuclide angiography, stress thallium scintigraphy, coronary angiography and PET studies with N-13 ammonia and FDG at rest. The myocardial region with the maximum counts on the stress thallium study was used as the normal reference region for relative ammonia and FDG uptake. From matched ammonia and FDG short-axis images, a total of 156 regions were analyzed in ICM patients and 144 regions in NICM patients. Regional blood flow less than 85% in both thallium and ammonia studies was considered abnormal. FDG:ammonia ratio of ≥1.2 was considered to represent metabolism-blood flow mismatch.

	abnormal flow	mismatch	match	LVEF (%)
ICM	89 (57%)*	37 (47%)	52 (53%)	16 ± 8
NICM	37 (26%)*	4 (11%)	33 (89%)	12 ± 5

*$p < 0.001$, **$p < 0.005$

In ICM patients, 57% of all regions demonstrated abnormal blood flow and almost half of such regions exhibited preserved glucose extraction indicative of ischemic but viable myocardium. In contrast, approximately one-fourth of NICM regions had decreased regional blood flow and the majority (89%) of such regions had matched decrease in glucose extraction (nonischemic). Thus, despite the absence of significant epicardial coronary artery stenosis, decreased regional blood flow occurs in patients with NICM and may reflect regions with admixture of viable myocytes and fibrosis.

965-48 Ejection Fraction and Wall Thickness Correlate with Impaired Energy Metabolism in Patients with Dilated Cardiomyopathy

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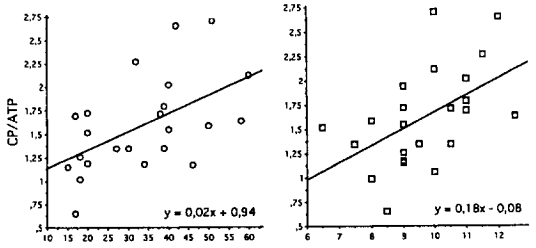
Using 31P-MR spectroscopy, abnormalities of cardiac energy metabolism have been demonstrated in patients with dilated cardiomyopathy (DCM). However, a detailed analysis of the correlations among energy metabolism, cardiac hemodynamics and myocardial hypertrophy obtained from 31P-MR, right and left heart catheterization and echocardiography has not been presented. 23 patients with DCM (left ventricular (LV) EF 34 ± 3%; NYHA class 2.7 ± 0.1; SE) underwent right and left heart catheterization and echocardiography ± 3 days before/after MR spectroscopy. Coronary artery disease was ruled out by coronary angiography. ECG-triggered, localized 31P-MR spectra from the anteroseptal myocardium were acquired at rest (prone position) during 30 min on a 1.5 T Philips Gyroscan MR system using ISIS localization, adiabatic pulses, and a 15 sec repetition time. Peak areas were corrected for T1 effects and for blood contamination, and were determined with Lorentzian line fits in the time domain. Linear correlations between creatine phosphate (CP)/ATP ratios and hemodynamic parameters were calculated.



LV pressures and diameters, cardiac output, stroke volume, pulmonary arterial pressures, right atrial pressure and pulmonary arterial oxygen saturation did not correlate with CP/ATP. Thus, our data demonstrate that in DCM, the extent of high-energy phosphate depletion is related to the extent of mechanical dysfunction as well as to LV wall thickness.

965-49 Abnormal Mitochondrial Respiration in Myocardium of Dogs with Chronic Heart Failure

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We previously showed that abnormalities of mitochondria (MIT) exist in the failing heart and include hyperplasia, reduced organelle size and structural injury. In the present study, we examined MIT respiration in LV tissue obtained from 11 normal (NL) dogs and 8 dogs with heart failure (HF) produced by intracoronary microembolizations (LV ejection fraction 23 ± 3%). Tissue specimen (30 mg) were obtained from the subendocardial (ENDO) and subepicardial (EPI) halves of the LV wall. Basal (V_o) and state 3 (maximal) respiration (V_{ADP}, after addition of 1 mM ADP) were measured with an oxygraph and Clark electrode using saponin skinned fiber bundles (0.2–0.3 mm). Respiratory rate was calculated in ngatoms of oxygen/min/mg of noncollagen protein. The respiration control ratio (RCR) was calculated as V_{ADP}/V_o.

	V_o		V_{ADP}		V_{ADP}/V_o	
	ENDO	EPI	ENDO	EPI	ENDO	EPI
NL	9 ± 2	7 ± 1	46 ± 6	47 ± 1	6 ± 1	7 ± 1
HF	6 ± 1	6 ± 1	20 ± 5	22 ± 5	4 ± 1	4 ± 1
P-value	<0.07	<0.5	<0.001	<0.005	<0.04	<0.004

MIT state 3 respiration is significantly reduced in myocardium of dogs with chronic HF. The observed reduction in the RCR confirms the presence of injury to inner MIT membrane. The abnormalities in MIT oxygen utilization support the concept of low energy production in the failing heart.

965-50 Accumulation of Collagen in the Cardiac Interstitium of Dogs with Chronic Heart Failure is Associated with Decreased Capillary Density and Increased Oxygen Diffusion Distance

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Progressive LV dysfunction is a characteristic feature of the failing heart. The mechanism(s) responsible for this functional deterioration are not known. Progressive accumulation of collagen in the cardiac interstitium termed "reactive interstitial fibrosis" (RIF), occurs in the failing heart but its role in the progression of LV dysfunction remains uncertain. We examined the consequences of RIF severity on capillary density (CD) and oxygen diffusion distance (ODD) in LV myocardium of 11 dogs with heart failure produced by intracoronary microembolizations (LV ejection fraction 26 ± 1%). CD was defined as the index capillary to fiber ratio and ODD as half the distance between two adjoining capillaries. Frozen sections were prepared from LV tissue and double stained with a collagen III antibody to quantitate RIF and with GSI lectin to visualize capillaries. From each section, 5 infarct free fields manifesting severe RIF (volume fraction 16 ± 2%) and 5 fields with little or no RIF (volume fraction 4 ± 1%) were selected for analyses.

	No RIF	RIF	Probability
CD	1.05 ± 0.03	0.92 ± 0.02	$P < 0.003$
ODD (μm)	2.3 ± 0.4	15.3 ± 0.4	$P < 0.001$

Conclusion: In the failed canine heart, CD is decreased and ODD is increased in LV regions manifesting severe RIF. These abnormalities may contribute to the progression of LV dysfunction by promoting hypoxia of the collagen encircled cardiocytes.

965-51 Daily Coronary Microembolization in Awake Dogs Leads to Heart Failure

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Previous efforts to induce heart failure using percutaneous coronary embolization required multiple surgical procedures and a prolonged time course (3–6 months) until heart failure develops. The goal of this study was to create a reproducible and more rapid model of ischemic heart failure in dogs using repeated coronary embolization via a chronically implanted coronary catheter. Dogs (n = 5) were chronically instrumented for measurements of mean arterial pressure (MAP), left ventricular pressure (LVP) and left atrial pressure (LAP). After full recovery, hemodynamic measurements and the response of LV dp/dt to increasing doses of isoproterenol were performed weekly. After control experiments, glass microspheres (90 μm diameter) were injected into coronary circulation daily (50,000–100,000/day) using the implanted coronary catheter for approximately two weeks. The hemodynamic measurements after 3 weeks and a total of 925,000 ± 250,000 microspheres are shown as follows (* < 0.05 from control).

	Control	3 Wks of Embolization
LVP (mmHg)	133 ± 6	106 ± 2*
LVEDP (mmHg)	3.8 ± 1.2	14.2 ± 0.9*
MAP (mmHg)	101 ± 2	87 ± 8
LAP (mmHg)	5.8 ± 1	11.7 ± 1*
HR (beats/min)	86 ± 9	138 ± 32
LVdP/dt(mmHg/s)	3109 ± 665	2281 ± 460*

The dose response curves of LVdP/dt to Isoproterenol (0.025, 0.05, 0.1, 0.5 μg/kg) were significantly shifted down and to the right after heart failure. Clinical signs of heart failure such as protein wasting, dyspnea, edema and ascites developed in all animals. Thus, an ischemic heart failure, as defined by hemodynamic, pharmacological and clinical features, developed using daily coronary embolization.

965-52 Relationship Between Heart Chymase and ACE Activity in Dogs with Volume Overload Hypertrophy and Increased Cardiac Angiotensin Peptide Levels

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We have previously reported increased intracardiac angiotensin II (ANG II) levels in a dog model of volume overload hypertrophy produced by percutaneous chordal rupture of the mitral valve. Whether the increase in ANG II is mediated by angiotensin converting enzyme (ACE) and/or heart chymase is unknown. Magnetic resonance imaging and high-fidelity pressure monitoring were performed on 8 adult mongrel dogs before and 5 months after causing mitral regurgitation (MR). Left ventricular (LV) end-diastolic volume increased from 58 ± 13 [SD] to 102 ± 35 ml ($p < 0.001$), as did end-systolic volume (33 ± 10 to 47 ± 18 ml, $p < 0.001$). LV mass increased in all dogs from 82 ± 22 to 112 ± 25 grams ($p < 0.001$) and the LV mass/end-diastolic volume ratio decreased significantly from 1.63 ± 0.20 to 1.17 ± 0.23 gm/ml ($p < 0.001$). ANG II levels were significantly higher in the midwall of the left ventricle in mitral regurgitation hearts than in normal controls (85 ± 39 vs. 27 ± 16 pg/gm, $p < 0.01$) and ANG II correlated with LV end-diastolic wall stress ($r = 0.75$, $p < 0.05$). ACE activity increased in MR hearts compared to controls (1.22 ± 0.46 vs. 3.55 ± 1.39 mUnits/gm, $p < 0.05$) and chymase activity was also in MR hearts compared to controls (9.42 ± 4.6 vs. 19.81 ± 8.93 nmol/gm/min, $p < 0.05$). These results demonstrate significant elevation of intracardiac ANG II levels associated with increasing diastolic stress and increasing intracardiac ACE and chymase activity. The parallel responses of ACE and chymase activity in response to volume overload of the dog heart suggest that the increased ANG II levels in this model are generated by ACE and chymase. Further studies using selective inhibitors of these enzymes are needed to establish an etiologic relationship between increased ACE activity and left ventricular remodeling in this model.

965-53 Myocardial Glycolytic and Fatty Acid Metabolism During Progression of Adriamycin (ADR)-Induced Heart Failure in Rats

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To investigate the changes in myocardial glycolytic and fatty acid metabolism during progression of ADR-induced heart failure, sixty five 8-weeks male S-D rats were injected intraperitoneally with ADR (15 mg/kg) or equivalent volume of saline, divided into 6 times for 2-weeks. Rats were sacrificed and the left ventricles were removed, at 1 day (ADR 1D group, Control 1D group), at 3 weeks (ADR 3W group, Control 3W group) and at 6 weeks (ADR 6W group, Control 6W group) after the last ADR or saline injection. By using proton-MRS, we measured myocardial metabolites (lactate and alanine as indices of glycolytic metabolism, and free carnitine as an index of fatty acid metabolism). As an index of energy production, high energy phosphate (ATP) in the myocardium was also measured by HPLC.

Results; The cumulative mortality rate was 0% in control groups and 48% in ADR-treated groups during observed period. The mortality rate was abruptly increased 3 weeks after the last injection.

	lactate	alanine	free carnitine	ATP
Control 1D (n = 6)	11.85 ± 0.98	1.12 ± 0.06	1.07 ± 0.08	8.52 ± 0.32
Control 3W (n = 6)	11.22 ± 0.91	1.14 ± 0.09	1.12 ± 0.09	8.60 ± 0.38
Control 6W (n = 4)	13.10 ± 1.68	1.58 ± 0.23	1.05 ± 0.12	8.90 ± 0.19

lactate, alanine, free carnitine, μmol/wet g, ATP, nmol/mg protein

No significant changes in tissue levels of lactate, alanine, free carnitine and ATP were observed among Control groups

	lactate	alanine	free carnitine	ATP
ADR 1D (n = 6)	15.72 ± 1.38	2.10 ± 0.23	1.05 ± 0.07	7.23 ± 0.51
ADR 3W (n = 6)	3.47 ± 0.41	1.02 ± 0.24	0.83 ± 0.05	5.98 ± 0.16
ADR 6W (n = 6)	9.10 ± 0.76	1.28 ± 0.17	0.60 ± 0.07	4.70 ± 0.38

In ADR 1D, the tissue levels of lactate and alanine were significantly higher than those of Control 1D ($p < 0.05$), although the tissue levels of free carnitine and ATP were preserved. However, in ADR 3W, the tissue levels of free carnitine and ATP were significantly lower than those of Control 3W ($p < 0.05$). The tissue levels of free carnitine and ATP appeared to be further reduced in ADR 6W.

Conclusion; This study demonstrated that the impaired energy production had already occurred even at early stage of ADR-induced heart failure.

966 Vascular Responses to Hypertension

Tuesday, March 21, 1995, Noon–2:00 p.m.
Ernest N. Morial Convention Center, Hall E
Presentation Hour: 1:00 p.m.–2:00 p.m.

966-39 Hypertension and Left Ventricular Hypertrophy Further Impair Utilization of the Reduced Coronary Reserve in Patients with Coronary Artery Stenosis

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Left ventricular hypertrophy (LVH) predisposes to an increased infarct size after coronary occlusion in dog. Aim of the study was to investigate the impact of the coexistence of LVH secondary to hypertension and coronary stenosis on the coronary vasodilator capacity in man. Coronary flow velocity in left anterior descending artery (LAD) was monitored by Transesophageal-Doppler at baseline and during low- and high-dose of i.v. Dipyridamole (0.56 mg/Kg/4 min followed after 2 min by 0.28 mg/Kg/2 min) in 56 patients, divided as follows: 19 normal controls (N Group), 21 pts with hypertension, LVH and no CAD (LVH Group), and 16 pts with moderate LAD artery stenosis (≤75%) [10 without LVH (LAD Group) and 6 with LVH secondary to hypertension (LAD + LVH Group)]. All pts had Dipyridamole Echo test negative for left ventricular asynergy. Blood pressure and left ventricular mass were similar in N vs LAD pts, and in LVH vs LAD + LVH. Mean total coronary flow velocity was measured from Doppler recordings. Coronary reserve was computed as the ratio of high-dose Dipyridamole to Basal flow velocity. Minimum coronary resistance and the percent of coronary reserve recruited after low-dose Dipyridamole were also computed.

Results: Baseline coronary flow velocity was 29 ± 6 cm/sec in N, and significantly higher in LVH and CAD (39 ± 11 and 41 ± 11, respectively, $p < 0.01$). Coronary flow velocity after high-dose Dipyridamole was 92 ± 18 in N, and significantly lower only in LAD + LVH (68 ± 16, $p < 0.05$). Coronary reserve was 3.3 ± 0.7 in N, and significantly reduced in all pts subgroups (2.4 ± 0.4, 2.2 ± 0.6, 2.3 ± 0.4 in LVH, LAD, LAD + LVH; $p < 0.01$ vs N). Percent of coronary reserve recruited after low-dose Dipyridamole was 94 ± 8% in N, 91 ± 11% in LAD, and lower in LVH (79 ± 11%, $p < 0.01$ vs N) and in LAD + LVH (69 ± 10%, $p < 0.05$ vs LVH). Compared to N, minimum coronary resistance was significantly higher in LVH ($p < 0.05$) and LAD + LVH ($p < 0.01$) (0.94 ± 0.2 vs 1.20 ± 0.3 and 1.40 ± 0.4 mmHg/ml/min, respectively); it was also higher in LAD + LVH than in LAD alone (1.07 ± 0.2 mmHg/ml/min, $p < 0.05$).

Conclusions: Coronary reserve is similarly reduced in pts with LVH secondary to hypertension, LAD stenosis alone, or LVH + LAD stenosis. Coexistence of hypertensive LVH with LAD stenosis is associated, compared to LAD stenosis alone, with significantly higher minimum coronary resistance and a hindered utilization of the reduced coronary reserve.

966-40 The Impact of Ambulatory Blood Pressure on Diastolic Dysfunction in Uncomplicated Hypertension

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Although arterial hypertension is the main determinant of diastolic dysfunction, few data exist about the relations between 24-h BP profile and LV filling. We examined Doppler echocardiography and ambulatory BP (ABP) in 101 subjects (60 men, 41 women, age 46.3 ± 9.9 years) free of cardiac drugs. Subjects were excluded for coronary artery and valvular disease, heart failure and diabetes. Based on clinic BP levels 18 subjects were considered